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Health and Environmental Effects Profile for Zineb

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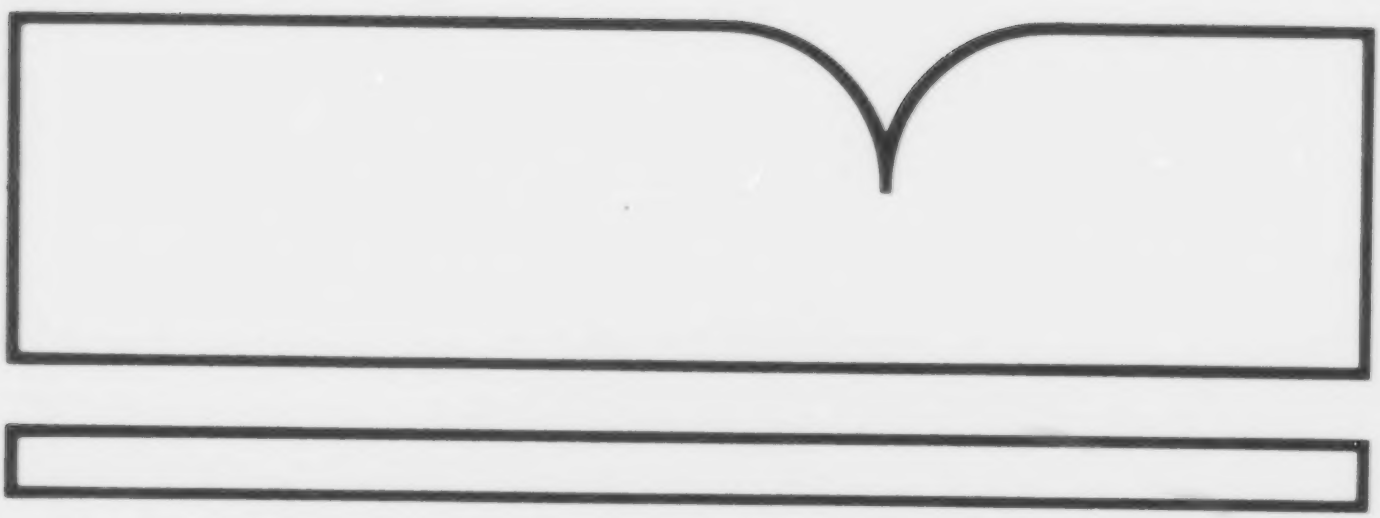

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR ZINEB

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
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16. ABSTRACT

The Health and Environmental Effects Profile for Zineb was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Zineb has been determined to be a systemic toxicant. An Acceptable Daily Intake (ADI), defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect, for Zineb is 5×10^{-2} mg/kg bw/day for oral exposure.

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched."

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include, Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor or q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA docket.

ACKNOWLEDGEMENTS

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LIST OF ABBREVIATIONS

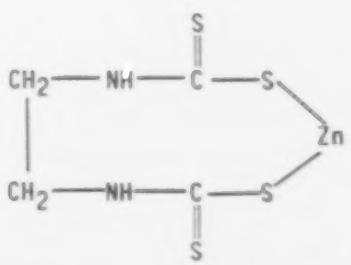
ADI	Acceptable Daily Intake
BCF	Bioconcentration factor
bw	Body weight
CNS	Central nervous system
DNA	Deoxyribonucleic acid
LC_{50}	Concentration lethal to 50% of recipients (and all other subscripted dosage levels)
LD_{50}	Dosage lethal to 50% of recipients (and all other subscripted dosage levels)
LOAEL	Lowest-observed-adverse-effect level
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
ppm	Parts per million
TLC	Thin layer chromatography
UV	Ultraviolet

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Zineb is the common name for [[1,2-ethanediylbis(carbamodithioato)]-(2-)]zinc, formerly [ethylenebis(dithiocarbamato)]zinc (Sanborn et al., 1977; BCPC, 1977). This compound is also known as zinc ethylenebisdithiocarbamate; 1,2-ethanediylbiscarbamodithoic, zinc complex; 1,2-ethanediylbiscarbamothioic acid, zinc salt; [ethylenebis(dithiocarbamate)]zinc; ethylenebis(dithiocarbamato)zinc; [[1,2-ethanediylbis(carbamodithioato)](2-)]-S,S'-zinc (IARC, 1976).

This fungicide was first introduced in 1943 under the trade name of Dithane Z-78 by Rohm and Haas, and as Parzate-Zineb by E.I. DuPont de Nemours and Co. as an improvement of nabam (BCPC, 1977; Sanborn et al., 1977). Zineb is also known by numerous other trade names including: Aspor, Asporum, Bercema, Blightox, Blitex, Blizene, Carbadine, Chem Zineb, Cineb, Crittox, Cynkotox, Daisen, Dithane 65, Dithane Z, Dithiane Z-78, Ent 14,874, Ethyl Zimate, Hexathane, Kupratsin, Kypzin, Lirotan, Lonacol, Micide, Miltox, Novosir N, Novozin N50, Pamosol 2 Forte, Parzate, Parzate C, Perosin, Perosin 75B, Perozin, Perozine, Polyram Z, Sperlox-Z, Thiodow, Tiezene, Tritoftorol, Tsineb (Russian), Zebenide, Zebtox, Zidan and Zinosan (IARC, 1976; NIOSH, 1983). The structure of zineb (Ouellette and King, 1977) is given below:



Molecular formula: $C_4H_6N_2S_4Zn$

Molecular weight: 275.8

The Chemical Abstracts Service (CAS) Registry Number for this compound is 12122-67-7.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Zineb is a light-colored powder (BCPC, 1977; Sanborn et al., 1977) with the following physical properties:

Melting Point:	decomposes before melting (BCPC, 1977)
Vapor Pressure:	negligible at room temperature (no value given) (BCPC, 1977)
Solubility:	10 mg/ℓ in water at 20°C (Sanborn et al., 1977); soluble in chloroform, carbon disulfide and pyridine (IARC, 1976)
Stability:	unstable to heat and moisture (BCPC, 1977)
Bioconcentration Factor (estimated from water solubility):	169 (Kenaga, 1980)

1.3. PRODUCTION DATA

Zineb is produced in the United States by the Blue Spruce Co., Bound Brook, NJ; FMC Corp., Middleport, NY and Rohm and Hass Co., Philadelphia, PA (SRI, 1983). It is prepared by reacting the condensation product of ethylenediamine, carbon disulfide and sodium hydroxide with a zinc salt. Current United States production data are unavailable; however, an earlier report (Lawless et al., 1972) suggests that an average of 2.9 million pounds per year were produced from 1967-1969.

1.4. USE DATA

Domestic zineb usage in 1975 was estimated to be 3.3 million pounds (Ayers and Johnson, 1976). Zineb is used primarily to protect seeds and treat agricultural commodities such as fruits and vegetables for fungal diseases. Zineb is also used as a fungicide in fabrics, paints and surfaces to be painted (IARC, 1976).

2. ENVIRONMENTAL FATE AND TRANSPORT

Data for the fate and transport of zineb in soil are available from both laboratory and field studies. Helling et al. (1974) studied the mobility of zineb in a variety of soil types on TLC plates.

A 75% zineb (100 µg active ingredient) preparation applied to TLC plates of Hagerstown silty clay loam (2.5% organic matter content, 39.5% clay, pH 6.8, water content at 1/3 bar 34.1%) had an overall average R_f of 0.01 when visualized by bioassay using 10 different species of fungi and 1 alga. The R_f values for 1 µg of zineb on soil TLC plates with five soil types were as follows (the organic matter content is given in parentheses): 0.15 on Norfolk sandy loam (0.14%); 0.16 on Lakeland sandy loam (0.90%); 0.10 on Hagerstown silty clay loam (2.5%); 0.08 on Barnes clay loam (6.9%); and 0 on Celeryville muck (90.4%). Autoradiography confirmed that zineb was virtually immobile in soil.

Using 4-inch diameter soil columns of a mix of 50% peat moss and 50% Oakley loamy sand, Munnecke (1961) studied the mobility of a 1000 ppm active ingredient suspension of 65% zineb in water, using Myrothecium verrucaria spores for detection, and concluded that zineb has a low mobility in soil.

The fate of zineb in soil was studied by Nash and Beall (1980) when the fungicide was sprayed onto tomato plants growing in Galestown sandy loam (pH 6.7, organic matter content 5.2%) in microagroecosystem chambers. Zineb, detected as ethylenediamine, was present on the soil surface throughout the 70-day duration of the experiment. It did not penetrate below 1 cm depth, but dissipated with a half-life of 23 days. The concentration of ethylenediamine in leachate water was only 0.45 µg/ℓ.

Hubbell et al. (1973) reported that zineb applied by hand weekly for 12 weeks to plots of Norfolk loamy fine sand at a rate of 1.456 kg active ingredient/ha (1.3 lbs/acre) accumulated to a maximum level of 2.5 ppm in soil samples taken at biweekly intervals at a depth of 0-15 cm.

The low mobility or high adsorbency of zineb in soil is consistent with the soil adsorption coefficient (K_{oc}) of 1230 calculated from water solubility by Kenaga (1980).

Munnecke et al. (1962) found that zineb did not produce toxic vapors when air was passed through soil columns (mix of 50% peat moss and 50% Oakley loamy sand) treated with 500-2000 ppm of active fungicide in 50 ml of water; however, carbon disulfide was produced. The low volatility of zineb is consistent with its negligible vapor pressure.

In an abstract of a study from the Russian literature, Kovaleva and Talanov (1982) reported that 5 days after spraying 20 kg zineb/ha onto the soil surface, the concentration of zineb in the top 1 cm of soil was 10.9 mg/kg. This level declined to 0.03 mg/kg by 4 months. No mechanism of disappearance could be discerned from the abstract.

Little information regarding the degradation of zineb by microbes in the soil was available. Microbial degradation may represent a minor route, however, since zineb is readily decomposed by high moisture content (Sanborn et al., 1977).

The microbial metabolism of 5,6-dihydro-3H-imidazo(2,1-c)-1,2,4-dithiazole-3-thione, has been investigated. This chemical, a product of the spontaneous degradation of zineb, is commonly known as ethylenethiuram monosulfide. Ethylenethiuram was metabolized microbially to produce ethylenethiourea (ETU) (Vonk and Sijpesteijn, 1976), a carcinogen in animals (IARC,

1974, 1982). ETU was degraded to ethyleneurea and CO_2 both chemically and microbially within 4 days in soil (Kaufman and Fletcher, 1973).

The fate of zineb in aquatic media has been less well studied than that in soil. The main route of entry into water would probably be through soil particles in runoff water, consistent with its high K_{oc} and experimentally observed tendency to sorb tightly to soil.

Since zineb is rapidly hydrolyzed in moist soil (Sanborn et al., 1977), it is reasonable to assume that hydrolysis is a major route of transformation in aquatic systems as well.

Iley and Fiskell (1963) noted no difference in the rate of degradation of zineb exposed to sunlight or to darkness for as long as 19 months. No other information on the photolysis of zineb was found.

Information regarding the bioconcentration of zineb in aquatic organisms was not located in the available literature. The relatively low BCF of 169 calculated by Kenaga (1980) from water solubility data indicates that zineb may not substantially accumulate in biota.

Thus, zineb may enter the aquatic environment through soil runoff, where it will be hydrolyzed readily. One of the products of hydrolysis is ETU, but ETU is readily photodegraded in aqueous media to ethyleneurea, glycine sulfate and hydantoin in the presence of sensitizers (Cruickshank and Jarrow, 1973; Rhodes, 1977). In draining ditch water, ETU was 90% degraded by sunlight in 24 days (Ross and Crosby, 1973).

Information regarding the fate and transport of zineb in air is limited. Since the vapor pressure of zineb at room temperature is considered to be negligible (BCPC, 1977), volatilization is unlikely. Nash and Beall (1980) found the air concentrations of zineb (detected as ethylenediamine) to be only 20 ng/m³ at day 0 in the previously described microagroecosystem

chamber with a half-life of 11-14 days. The major routes of entry into the atmosphere are more likely to be spray drift during application and drift in wind of zineb sorbed to soil particles. It seems that the extent of degradation in air will depend upon the moisture content and hydrolysis may be the major route of transformation in air. Karageorgiev (1981) noted that the degradation of zineb sprayed onto pears was faster when the humidity was high than when it was low. The degradation half-life was determined to be 5.5-10 days.

3. EXPOSURE

No monitoring data for zineb were contained in STORET, and no other information regarding ambient levels of zineb in soil, water or air was available.

Besides occupational exposure, human exposure to zineb occurs primarily through residues on food. Duggan et al. (1966) monitored food for pesticides using the "total diet" approach (all the food consumed over a 2-week period by an 18-year-old male). These investigators collected 82 foods from 18 markets in Boston, MA, Kansas City, MO and Los Angeles, CA, separated them into 12 classes and combined them into a slurry. Of 216 composites, 5 were found to contain dithiocarbamate residues ranging from 0.4-0.8 ppm calculated as equivalent zineb concentrations. These foods were mainly grain and cereal products, and raw and processed leafy vegetables.

Concern over exposure to zineb residues on food is enhanced by the increased levels of ETU found in cooked and processed foods. Little, if any, residual ETU was found on harvested apples, tomatoes, grapes, pears, potatoes, cucumbers, squash or cantaloupes; however, the acts of cooking, processing or storing such foods have resulted in detectably increased levels of ETU (Ross et al., 1978; Ripley and Cox, 1978; Ripley et al., 1978; Ripley and Simpson, 1977; Pease and Holt, 1977; Watts et al., 1974).

4. PHARMACOKINETICS

4.1. ABSORPTION

Measurements of the 24-hour food intake in rats administered zineb in their feed at a level of 396 or 9130 ppm and measurements of zineb in 24-hour fecal excreta along with estimates of hydrolysis during this time indicated that at least 11-17% of the administered dose was absorbed by the gastrointestinal tract (Blackwell-Smith et al., 1953). Two hours after the administration of an oral dose of 1 g zineb/kg, carbon disulfide was detected in the expired air of Wistar rats (Truhaut et al., 1973). Jordan and Neal (1979) found that the majority (63%) of the orally administered radioactivity (0.25 mmole ^{14}C-zineb/kg) was eliminated in the 48-hour feces of ND/4 (s) BR mice, while only ~6% was recovered in the 48-hour urine. The total amount of radioactivity recovered from all sources was 65.1% of the administered dose.

4.2. DISTRIBUTION

Pertinent data regarding the distribution of zineb in animal tissues were not located in the available literature.

4.3. METABOLISM

The major metabolites of zineb excreted in the urine of 50 male and female Wistar rats receiving an oral dose of 1 g zineb/kg 3 times/week for 2 weeks were identified as ethylenebisisothiocyanato sulfide and ethylenethiourea (ETU). Carbon disulfide was identified as an expired metabolite (Truhaut et al., 1973).

The amounts of urinary metabolites expressed as percent of radioactivity in urine from ND/4 (s) BR mice given 0.25 mmole ^{14}C-zineb/kg (the position of the ^{14}C-label was not specified) were: 15.2% ETU, 1.0% ethyleneurea, 81% polar (i.e., more polar than ethyleneurea) and 2.7% less polar than ethyleneurea metabolites (Jordan and Neal, 1979).

4.4. EXCRETION

Of 65.1% recovered radioactivity from mice fed ^{14}C-zineb (the position of the ^{14}C-label was not specified), 96.5% was excreted in 0-24 hours and 3.5% in 24-48 hours. The majority (90.4%) of the recovered dose was found in the feces, while the urine accounted for only 9.6%. None of the ^{14}C-zineb was excreted as $^{14}CO_2$ (Jordan and Neal, 1979). Two hours after dosing rats with zineb, carbon disulfide was detected in the expired air (Truhaut et al., 1973).

5. EFFECTS

5.1. CARCINOGENICITY

Two hybrid strains of mice, B6C3F1 and B6AKF1, were given 464 mg zineb/kg daily (the maximum tolerated dose, which was determined from the average body weight of mice and not corrected for weight gain) by gavage from day 7 to day 28 of age, after which zineb was given in the diet at a level of 1298 ppm for 85-89 weeks. Negative controls consisted of untreated and vehicle treated mice of both sexes of both strains. After 86-90 weeks, the mice were killed and necropsied. Total tumor incidences for B6C3F1 mice were 5/18 treated males and 1/18 treated females versus 22/79 control males and 8/87 control females. Hepatomas were found in 4/18 treated males compared with 8/79 control males. Pulmonary adenoma was present in 1/18 treated females and 3/87 control females. One reticulum cell sarcoma was found in treated males, compared with 5/79 control males. For strain B6AKF1 mice, total tumor incidences were 4/17 treated males and 3/18 treated females, compared with 16/90 control males and 7/82 control females. Hepatomas were present in 2/17 treated males, compared with 5/90 control males. Of 17 treated males, one had pulmonary adenoma and one had reticulum cell sarcoma; the incidences of these tumor types in male control mice were 9/90 and 1/90, respectively. Of 18 treated females of this strain, 2 had pulmonary adenomas and 1 had reticulum cell sarcoma. The incidence of each of these tumors in female controls was 3/83. None of these tumor incidences was significantly different from controls (BRL, 1968; Innes et al., 1969).

Chernov and Khitsenko (1969) administered zineb to 101 strain A mice and 79 C57B1 mice in weekly oral doses of 3500 mg/kg for 6 weeks. After 3 months, the animals were killed and examined for tumors. The incidences of pulmonary adenoma were 35/100 in treated and 30/97 in control strain A mice,

and 6/79 treated and 0/87 control C57B1 mice. When 1750 mg zineb/kg was given for 11 weeks to C57B1 mice killed after 6 months, 2/29 mice had pulmonary adenomas compared with 0/59 controls.

B6C3F1 and B6AKF1 mice (18 mice/sex/strain) were given one time subcutaneous injections of 1000 mg zineb/kg in gelatin on the 28th day of age and were killed after 18 months (BRL, 1968). For B6C3F1 mice, total tumor incidences were 7/18 treated males, 1/18 treated females, 27/141 control males and 9/154 control females. The incidence of reticulum cell sarcoma in treated males was 5/18 compared with 8/141 in control males. Pulmonary adenomas were seen in 2 treated males, 1 treated female, 10 control males and 4 control females. For B6AKF1 mice, 3/18 treated males and 3/18 treated females, 8/161 control males and 17/157 control females had tumors. For the treated animals, these consisted of 2 reticulum cell sarcoma-bearing and 1 pulmonary adenoma-bearing females, and 1 pulmonary adenoma-bearing and 1 hepatoma-bearing male. The incidence of these tumors in controls were: reticulum cell sarcoma - 5/157 females, 0/161 males; pulmonary adenoma 10/157 females, 6/161 males; hepatomas - 0/157 females, 1/161 males. None of these incidences differed significantly from controls.

Blackwell-Smith et al. (1953) administered zineb to 10 male and 10 female rats/group at dietary levels of 0, 500, 1000, 2500, 5000 and 10,000 ppm for up to 2 years. Upon necropsy, malignant tumors were observed at all dose levels with the following frequencies: for controls - 1 lung tumor in males, 1 lung adenocarcinoma in females; for the 500 ppm group - 2 lung tumors in males; for the 1000 ppm level - 3 malignant lung tumors in males, 1 mammary carcinoma in females; for the 2500 ppm level - 2 malignant lung tumors in males, 1 thyroid papillary adenocarcinoma; for the 5000 ppm group - 1 lung tumor in males; and for the 10,000 ppm - 1 malignant tumor of lung

and small bowel in males. These tumors did not appear to be treatment-related (Blackwell-Smith et al., 1953).

Of 60 rats given zineb twice a week by gavage for 22 months at a dose level of 285 mg/kg, the incidence of tumors in the 10 surviving rats was 1/10 with adenocarcinoma and 1/10 with lymphosarcoma of the intestine. A fibrosarcoma was present in 1/46 control rats (Andrianova and Alekseev, 1970). In rats receiving a subcutaneous implant of zineb at a dose of 20 mg/kg, 6/48 survived after 22 months. Tumor incidences were: hepatoma, 1/6; fibrosarcoma, 1/6; spindle cell sarcoma, 1/6; and rhabdomyosarcoma, 1/6. A fibrosarcoma was observed in 1/46 untreated controls (Adrianova and Alekseev, 1970).

As reviewed by IARC (1976), Kvitnitskaya and Kolesnichenko (1971) found lung adenomas in 6/20 4-month-old strain A mice exposed to zineb prenatally. The dams had received an intraperitoneal injection of 4 mg zineb/animal during the second half of pregnancy. No lung adenomas were observed in 4-month-old, strain A control mice.

5.2. MUTAGENICITY

Zineb has been tested for mutagenicity in bacterial systems, fungal systems, rat cell cultures and human cell cultures (De Lorenzo et al., 1978; Shiau et al., 1980; Waters et al., 1982; Morpurgo et al., 1979; Rocchi et al., 1980). These studies are summarized in Table 5-1. Zineb was not mutagenic in the reverse mutation assay in Salmonella typhimurium (De Lorenzo et al., 1978; Shiau et al., 1980; Waters et al., 1982) or in Escherichia coli (Waters et al., 1982), but it was positive in the reverse mutation assay in some strains of Bacillus subtilis and was positive in lethal DNA damage assays without, but not with, metabolic activation (Shiau et al.,

TABLE 5-1

Mutagenicity Testing of Zineb

Assay	Indicator Organism	Application	Concentration or Dose	Activation System	Response*	Comment	Reference
Reverse mutation	S. typhimurium TA1535	plate incorporation	NR	±S9	=	NC	De Lorenzo et al, 1978
	TA1537			±S9	=		
	TA1538			±S9	=		
	TA98			±S9	=		
	TA100			±S9	=		
Reverse mutation	S. typhimurium TA1535	liquid incubation	50, 100 or 300 µg/plate		+/-	+/- = increased number of mutants was <2-fold	Shiau et al., 1980
	TA100			±S9	+/-		
				±S9	-		
					-		
Reverse mutation	S. typhimurium 5 strains	plate incorporation	6 concentrations up to 10 mg/plate	±S9	-	NC	Waters et al., 1982
					-		
Reverse mutation	Escherichia coli WP_2uvrA	plate incorporation	6 concentrations up to 10 mg/plate	±S9	-	NC	Waters et al., 1982
					-		
Reverse mutation	Bacillus subtilis TKJ5211	spot test	50, 100 or 300 µg/plate	±S9	-	+For strain TKJ6321 ≥2-fold increase in number of mutations at 300 µg/plate; +++ = >2-fold at 50 µg/plate	Shiau et al., 1980
	TKJ6321			±S9	-		
					+		
					+++		
Lethal DNA damage	B. subtilis	spot test	50, 100 or 300 µg/plate	±S9	+	+ = inhibition zone >1 mm only at 300 µg/plate; +++ = inhibition zone >1 mm at ≥50 µg/plate	Shiau et al., 1980
					+++		
Unscheduled DNA synthesis	human lung fibroblast	cell culture	NR	±S9	-	Mancozeb was tested as two different products: Dithane M-45 and Manzate 200. Dithane M-45 gave a negative response. Manzate 200 was positive without metabolic activation, negative with metabolic activation.	Waters et al., 1982
					+		

*Responses: +, positive; -, negative; =, negative with and without S9 activation system; ±, positive with and negative without S9 activation system; ∓, negative with and positive without S9 activation system

NC = No comment; NR = Not reported

1980). Zineb also showed a positive response as enhanced mitotic recombination in Saccharomyces cerevisiae with or without microsomal enzyme preparations (Waters et al., 1982). Rocchi et al. (1980) demonstrated that zineb was an effective inhibitor of scheduled DNA synthesis in rat thymus cells and human lymphocytes in vitro. Unscheduled DNA repair in human cells in vitro was not affected by zineb treatment (Rocchi et al., 1980; Waters et al., 1982). Details of these studies are given in Table 5-1.

5.3. TERATOGENICITY

Pregnant rats and mice were given zineb at oral doses of 0, 200, 632 or 2000 mg/kg from day 6 of gestation until 1 day before Caesarian delivery (the time of delivery was not mentioned in the available abstract) (Short et al., 1980). No effect on fetal survival was observed, but reduced body weights were observed in rat fetuses at the 2000 mg/kg level. Significantly increased incidences of hydrocephalus, split centra, incomplete ossification of frontal bones, and enlarged occipital fontanel were also observed in the high dose group of rats. At this dose level of zineb, the dams had decreased body weights and food consumption. No effects were seen in mice.

Petrova-Vergieva and Ivanova-Chemishanska (1973) studied the teratogenic effects of zineb in pregnant rats. Groups of 9 rats received a single oral dose of 500-8000 mg zineb/kg on day 11 or 13 of pregnancy. The control group consisted of 14 untreated pregnant rats. There was a dose-related response for malformations in the fetuses at ≥2000 mg zineb/kg administered on day 11, progressing in severity from short, kinky tail at 2000 mg/kg to exencephaly and clubbed limbs at 4000 mg/kg, to encephalocele, cleft palate, cleft lip and micrognathic at 8000 mg/kg. Similar results were obtained when zineb was given on day 13 of pregnancy and the incidences of the abnormalities were even greater, with all 41 viable fetuses having malformations. No effects were seen at 1000 mg zineb/kg.

In another experiment these investigators fed zineb to pregnant rats at daily oral doses of 125, 250, 500 and 1000 mg/kg from day 2-22 of pregnancy, or exposed the rats to an atmosphere of 100 mg zineb/m^3 for 4 hours/day from day 4 of pregnancy until delivery. No teratogenic or embryotoxic effects were observed (Petrova-Vergieva and Ivanova-Chemishanska, 1973).

5.4. OTHER REPRODUCTIVE EFFECTS

Male rats were fed 1000 mg zineb/kg in peanut oil for 30 days, after which they were killed. Pathological changes were observed in the testes including damaged seminiferous tubules filled with necrotic cells (Raizada et al., 1979). Exposure of male rats to zineb at oral doses of 30 mg/kg, 6 days/week for 3 months caused ultrastructural changes in the seminal vesicles (Latalski and Obuchowska, 1980).

Zineb had no effect on the uterine or placental functions of decidualized pseudopregnant rats or on fetal survival in pregnant rats fed at dietary levels of $\leq$2500 ppm from day 6-9 of pseudopregnancy or from day 6-15 of pregnancy (Sing and Spencer, 1981).

Female rats given 2 oral doses of 260 mg zineb/kg at a 2-week interval had decreased weights of the uterus and ovaries, decreased durations of proestrus, estrus and metestrus and increased diestrus (Ghizelea and Ozeranschi, 1973). Makletsova (1979) reported that female workers exposed to zineb during its manufacture had increased frequency of spontaneous abortions (16.1% versus 8.1% in nonexposed workers) and increased frequency of pathological pregnancies (69.3% versus 57.3%). Complications in childbirth were increased from 61.5-73.4%. Only an abstract of this Russian study was available for evaluation.

5.5. CHRONIC AND SUBCHRONIC TOXICITY

The effects of chronic exposure to zineb have been studied in rats and dogs by Blackwell-Smith et al. (1953). In addition, several studies on the effects of subchronic administration of zineb to rats were encountered (Przezdziecki et al., 1969; Ivanova-Chemishanska et al., 1975; Blackwell-Smith et al., 1953).

Blackwell-Smith et al. (1953) administered zineb to 10 male and 10 female rats/group at dietary levels of 0, 500, 1000, 2500, 5000 and 10,000 ppm for 2 years, after which time all survivors were killed. Gross and histological examinations were performed on heart, lung, thyroid, liver, stomach, spleen, kidney, adrenals, large and small intestine and gonads. Hematological parameters examined at 11 and 22 months included red blood cell counts, hemoglobin concentrations and differential white cell counts, and were all within normal limits. Mortality was increased in female rats at the 5000 and 10,000 ppm levels. Thyroid hyperplasias were observed and graded for 0-5+ for severity. Severity of 2+ was seen in 6/17 control animals. Severity of $\geq$3+ was not present in any control animals but the incidences in treated rats were: 5/16 (3+), 1/16 (4+) at 500 ppm; 14/17 (3+), 1/17 (5+) at 1000 ppm; 7/14 (3+), 5/14 (4+) at 2500 ppm; 4/14 (3+), 8/14 (4+) and 1/14 (5+) at 5000 ppm; and 4/18 (3+), 11/18 (4+) and 3/18 (5+) at 10,000 ppm levels. In addition, renal congestion, nephritis, or nephrosis was observed in 6/19 treated animals at the 10,000 ppm, 1/14 at 5000 ppm, 1/14 at 2500 ppm, 1/17 at 1000 ppm and 0/16 at the 500 ppm level.

Blackwell-Smith et al. (1953) also fed zineb to nine mongrel dogs (three dogs/group) at dietary levels of 20, 2000 or 10,000 ppm for 1 year, after which time they and five untreated dogs were killed for histological examination of tissues. Dogs receiving 10,000 ppm had enlarged thyroids and

hyperplastic changes of 3+ severity. No other abnormalities were seen in this or other exposure level groups.

Przezdziecki et al. (1969) fed zineb to female Wistar rats in the diet at 117.5, 163 or 158.6 mg zineb/kg bw for 7 months. Upon necropsy, the researchers observed that zineb at all dose levels caused significant increases in thyroid weights and decreases in kidney, adrenal and ovary weights.

Zineb was administered by gavage in an aqueous suspension twice a week to groups of 35 Wistar rats at doses of 0, 96 or 960 mg/kg for 4.5 months, after which time 25 rats from each group were killed and their thyroid glands examined (Ivanova-Chemishanska et al., 1975). Ten rats/group were given an intraperitoneal injection of 1 μ Ci ^{131}I 5 days after the final dose of zineb. Only the high-dose rats had significantly increased ^{131}I uptake over control ($P<0.05$). The thyroids of the high-dose group were enlarged with many microfollicles, which were ~28% larger than the microfollicles in thyroids from control rats ($P<0.01$). Thyroid cells were observed to be columnar with vesicular nuclei and vacuolated cytoplasm.

Thyroid hyperplasia was seen in groups of male and female albino rats fed a diet containing 10,000 ppm zineb for 30 days. This effect did not occur at dietary levels of <5000 ppm (Blackwell-Smith et al., 1953).

Thus, zineb was shown to produce thyroid hyperplasia in rats and dogs when administered at high oral doses chronically and subchronically.

5.6. OTHER RELEVANT INFORMATION

The oral LD_{50} of zineb in rats was >5200 mg/kg (Blackwell-Smith et al., 1953) and was reported as 9600 mg/kg by Ivanova-Chemishanska et al. (1975). Other biological effects attributed to zineb exposure are acute poisoning in mice, chickens, rabbits, sheep, pigs and calves (exposures were

not given in the abstract of this Russian study) resulting in congestive hyperemia, hemorrhaging and serous edema, dystrophy and gastrointestinal inflammation (Evodokimov et al., 1980). In addition, zineb has been shown to cause reduction of rat microsomal metabolism of aminopyrine and alanine, reduced cytochrome P-450 content, and elevated cytochrome P-420 content at 1 mmole/kg in a single oral dose (Miladi et al., 1981) or at dietary levels of 600 ppm for 4 weeks (Pelissier et al., 1981). Lowy et al. (1977) calculated that the NOEL for the metabolic enzyme inhibition was $<74 \pm 15$ ppm for 4 weeks. Zineb also decreased pituitary gonadotropin content in rats at 1/10 the LD_{50} (Bentue-Ferrer et al., 1981), and caused CNS effects associated with enzyme changes in rats at doses of 1-10 g/day for 10 days (Godlewski, 1981; Maziarz, 1981) or at 1/10 LD_{50} for 6 days (Bainova et al., 1980).

6. AQUATIC TOXICITY

6.1. ACUTE

The acute toxicity of the fungicide, zineb, was tested in several species of fish. As noted in Table 6-1, the rainbow trout was the most sensitive fish species reported. The 24-, 48- and 96-hour LC_{50} values for this species, Salmo gairdneri, were 37.5, 28.0 and 20.8 mg zineb/ℓ, respectively (Schneider, 1979). Spehar et al. (1982) reported that the 48-hour LC_{50} values for carp, goldfish, medaka and the pond loach all exceeded 40 mg zineb/ℓ. The harlequin fish, Rasbora heteromorpha, had 24-, 48- and 96-hour LC_{50} values of 560.0, 400.0 and 250.0 mg zineb/ℓ, respectively (McKim et al., 1976; Tooby et al., 1975). Carp, Cyprinus carpio, exposed to 5.0 mg zineb/ℓ for 6 days showed no toxic effects (Antychowicz et al., 1979).

Zineb at 10 mg/ℓ caused 100% mortality in shrimp (species not specified) (Kasymov et al., 1981). In the water flea, Daphnia magna, 40 mg zineb/ℓ caused 50% lethality after a 48-hour exposure (Semov and Iosifov, 1973). Nishiuchi and Yoshida (1972) reported that all 48-hour LC_{50} values for four freshwater snail species, Indoplanorbis exustus, Cypangopaldina malleata, Physa acuta and Semisulcospina libertina, exceeded 100 mg zineb/ℓ. The 48-hour LC_{50} for the oligochaete worm, Tubifex tubifex, was reported to be 0.27 mg/ℓ (Voronkin and Loshakov, 1973).

6.2. CHRONIC

Zineb at 1.0-1.5 mg/ℓ was found to inhibit growth and cause morphological changes in Xenopus laevis (Amphibian) embryos (Bancroft and Prahlad, 1972). Growth was retarded, melanogenesis reduced and notochord development and structure altered in treated embryos.

TABLE 6-1

Acute Lethal Effects of Zineb to Fish

Species	Duration	Concentration (mg/ℓ)	Method	Effect	Reference
Rainbow trout, *Salmo gairdneri*	24 hours	37.5	NR	LC_{50}	Schneider, 1979
	48 hours	28.0	NR	LC_{50}	
	96 hours	20.8	NR	LC_{50}	
Carp, *Cyprinus carpio*	6 days	5.0	NR	None	Antychowicz et al., 1979
Carp, *Cyprinus carpio*	48 hours	>40.0	NR	LC_{50}	Spehar et al., 1982
Goldfish, *Carassius auratus*	48 hours	>40.0	NR	LC_{50}	Spehar et al., 1982
Medaka	48 hours	>40.0	NR	LC_{50}	Spehar et al., 1982
Pond loach, *Misgurnus*	48 hours	>40.0	NR	LC_{50}	Spehar et al., 1982
Harlequin fish, *Rasbora heteromorpha*	96 hours	250.0	NR	LC_{50}	McKim et al., 1976
Harlequin fish, *Rasbora heteromorpha*	24 hours	380	constant-flow	LC_{10}	Tooby et al., 1975
	24 hours	560	constant-flow	LC_{50}	
	48 hours	320	constant-flow	LC_{10}	
	48 hours	400	constant-flow	LC_{50}	
	96 hours	150	constant-flow	LC_{10}	
	96 hours	250	constant-flow	LC_{50}	

NR = Not reported

6.3. PLANT EFFECTS

The effects of zineb on the growth rate of the green alga, Scenedesmus acutus, were tested over a 5-day period. Zineb at concentrations of 0.5, 5.0, 10.0 and 100 mg/ℓ caused growth rates (detected by optical density) to be 97.9, 91.6, 83.3, 64.5 and 62.5% of control cultures after the 5-day exposure period (Krishnakumari, 1977). Zlateva (1977) reported that the 2-week LC_{50} of zineb was 10.0 mg/ℓ for Scenedesmus quadrica. Zineb was also reported to inhibit growth and heterocyst differentiation in the nitrogen-fixing blue-green alga, Nostoc muscorum.

6.4. RESIDUES

Belamie et al. (1977) reported detecting residues of dithiocarbamate fungicide in fish, predominately in the liver and kidney, and in river sediment in areas where fields are treated with the fungicides.

6.5. OTHER RELEVANT INFORMATION

An abstract of a study (Kasymov et al., 1980) from the Russian literature reported that the maximum permissible concentration of zineb for fisheries of that country was 0.0001 mg/ℓ. This level was established in conjunction with toxicity testing in a shrimp, Palaemon elegans, a mollusk, Cerastoderma lamarcki and two fish, Persian sturgeon and carp. Quantitative data on the toxicities were not reported in the available abstract.

7. EXISTING GUIDLELINES AND STANDARDS

7.1. HUMAN

Guidelines were located only in the available foreign literature. The maxiumum permissible concentration of zineb in air in the U.S.S.R. (Ryazanova et al., 1972) and in East Germany (Grigorowa et al., 1979) is 0.5 mg/m^3.

7.2. AQUATIC

An abstract of a study (Kasymov et al., 1980) from the Russian literature reported that the maximum permissible concentration of zineb for fisheries of that country was 0.0001 mg/ℓ. Other guidelines or standards for the protection of aquatic organisms from the toxic effects of zineb were not located in the available literature.

8. RISK ASSESSMENT

Zineb has been studied for its carcinogenic potential in mice and rats by oral and by subcutaneous exposures. The chronic and subchronic exposure studies resulted in tumor incidences that were not significantly different from controls. In one study, BRL (1968) reported an incidence of hepatomas of 4/18 in treated male mice, which was not statistically different from the incidence of 8/79 in control males. These animals were given zineb by gavage at a dose of 464 mg/kg from day 7-28 of age, and then were maintained on dietary levels of zineb of 1298 ppm for ~1.5 years. Also included in the study were female mice of this $B6C3F_1$ strain, and male and females of strain $B6AKF_1$. Reticulum cell sarcomas were also observed by these investigators (BRL, 1968), along with some hepatomas and adenomas following subcutaneous administration. Blackwell-Smith et al. (1953) observed malignant tumors in rats given dietary levels of zineb up to 10,000 ppm for 2 years, but they were unrelated to treatment. Some studies from the foreign literature were inadequate because of small numbers of animals, short durations or intermittent exposures. There is sufficient evidence that ETU, a degradation product and metabolite of zineb, is carcinogenic in experimental animals (IARC, 1974, 1982; 42 FR 40618). Moreover, the Carcinogen Assessment Group (CAG) of the U.S. EPA conducted a risk assessment for ethylenebisdithiocarbamate (EBDC) on the basis that a contaminant and metabolite, ETU, was carcinogenic (U.S. EPA, 1979). Because the ETU is also a metabolite and an environmental degradation product of zineb, further investigation of the potential carcinogenicity of zineb is desirable.

Sine the data are insufficient to indicate that zineb is an animal carcinogen, it is appropriate to derive an ADI value for zineb based on toxicity. A LOAEL can be obtained from the study of Blackwell-Smith et al.

(1953) in which rats were maintained on diets containing 0, 500, 1000, 2500, 5000 or 10,000 ppm zineb for 2 years. At a dose of 500 ppm, 5/16 rats had thyroid hyperplasia of 3+ severity and 1/16 rats had hyperplasia of 4+ (based on a scale of 0-5+), while control animals had hyperplasia of no >2+ with an incidence of 6/17. Both the incidence and severity of the thyroid hyperplasia increased with increasing dose. Thus, an ADI can be calculated to be 3.5 mg/human/day in the following manner:

$$ADI = 500 \text{ mg/kg food} \times 0.05 \times 70 \text{ kg} \div 500$$

For this calculation, the 500 ppm dietary level was expressed in terms of mg of zineb/kg of food and was multiplied by the fraction of the body weight consumed as food/day (0.05 for rats). An uncertainty factor of 500 was chosen because the 500 ppm dietary level represents a LOAEL, not a NOAEL, for rats; the effects observed were minimal and were also observed to a lesser degree in control animals; and the ADI is calculated for the most sensitive humans.

Zineb was also found to have teratogenic effects in rats exposed to $\geq$2000 mg/kg (Short et al., 1980; Petrova-Vergieva and Ivanova-Chemishanska, 1973), but this dose is much higher than the 500 ppm LOAEL in the Blackwell-Smith et al. (1953) study.

Statements concerning available literature in this document refer to published, quotable sources and are in no way meant to imply that confidential data, which this document could not address, are not in existence. These data, which are considered Confidential Business Information (CBI), are available in summary form as a CBI Appendix that can be accessed by individuals with appropriate clearance. Conclusions from the CBI Appendix regarding risk assessment, however, can be presented in this chapter.

The CBI Appendix to this document reviews subchronic and shorter-term animal studies on the toxic effects of oral exposure to zineb; the data from these studies support the above derivation of the ADI and provide additional evidence that zineb causes thyroid hyperplasia in rats.

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APPENDIX: LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of:

CA SEARCH (Files 308, 309, 310, 311, 320)
TOXLINE
MEDLINE
RTECS
SCI SEARCH
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
EPCASR
Chemical Industry Notes

Most of these searches were conducted in February, 1983; a few were conducted March-May, 1983. In addition, hand searches were made of Chemical Abstracts (Collective Indices 7 and 8th), and the following secondary sources were reviewed:

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